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REVIEW ARTICLE

Biomarkers: An Emerging Tool for Diagnosis of a Disease and Drug Development

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ABSTRACT:

Biomarkers provide a dynamic and powerful approach to understanding the spectrum of disease with applications in observational and analytic epidemiology, randomized clinical trials, screening and diagnosis and prognosis. Defined as alterations in the constituents of tissues or body fluids, these markers offer the means for homogeneous classification of a disease and risk factors, and the can extend our base information about the underlying pathogenesis of disease. A prerequisite for the clinical use of biomarker is elucidation of the specific indication, standardization of analytical methods, characterization of analytical features, incremental yield of different markers for given clinical indications. Biomarkers can also reflect the entire spectrum of disease from the earliest manifestations to the terminal stages. The major use of biomarkers in clinical investigation.

KEYWORDS: Diagnosis, Biomarker, Drug developments, Disease, Clinical Investigation.

1. INTRODUCTION:

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[1] Biomarker is a term often used to refer to a protein measured in blood whose concentration reflects the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other biological state of an organism. Biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers.[2]

Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human disease.[3] Although the term 'biomarker' is relatively new, biomarkers have been used in preclinical research and clinical diagnosis for some considerable time.

Blood pressure, for instance, is an example of an established surrogate endpoint biomarker – where a of an change in the biomarker can act as a substitute for a clinically meaningful observation – and became so due to the large epidemiological databases demonstrating a correlation between elevated blood pressures and adverse cardiovascular outcomes.[4] However, only a very small minority of biomarkers can be classed as surrogate endpoints and, although the identification of a surrogate marker is the 'holy grail' of biomarker research, this is by no means the only use for biomarker. Biomarker is relatively new; biomarkers have been used in pre-clinical research and clinical diagnosis for a considerable time.[5] For example, body temperature is a well-known biomarker for fever. Blood pressure is used to determine the risk of stroke. It is also widely known that cholesterol values are a biomarker and risk indicator for coronary and vascular disease, and that C-reactive protein (CRP) is a marker for inflammation. In practice, biomarkers include tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression, or outcome of treatment of disease. For the nervous system there is a wide range of techniques used to gain information about the brain in both the healthy and diseased state.[6,7] These may involve measurements directly on biological media (e.g., blood or

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cerebrospinal fluid) or measurements such as brain imaging which do not involve direct sampling of biological media but measure changes in the composition or function of the nervous system. A biomarker is a parameter that can be used to measure the progress of disease or the effects of treatment. The parameter can be chemical, physical or biological. In molecular terms biomarker is the subset of markers that might be discovered using genomics, proteomics technologies or imaging technologies. Biomarkers plays major role in medicinal biology. Biomarker brings the future things in our hand by helping in early diagnosis, disease prevention, drug target identification, drug response etc. Several diseased based biomarkers had been identified for many diseases such as serum LDL for cholesterol, blood pressure, P53 gene and MMPs for cancer etc.[8,9] Gene based biomarker is found to be an effective and acceptable marker in the present scientific world.

2. HISTORY OF BIOMARKERS:

The idea of using biomarkers to detect disease and improve treatment goes back to the very beginnings of medical treatment. The practice of uroscopy — examining a patient's urine for signs of disease — dates back to the 14th century or earlier, when practitioners would regularly inspect the colour and sediment of their patient's urine.

Philadelphia chromosome: In 1960, researchers discovered that some patients with chronic myelogenous leukaemia (CML), a form of adult leukaemia in which there is a proliferation of myeloid cells in the bone marrow, have a specific genetic change associated with their cancer, a shortened version of chromosome 22. This abnormality, known as the Philadelphia chromosome, is caused by a translocation between chromosomes 9 and 22. The consequence of this genetic swap is the creation of the BCR-ABL 'oncogene'; this cancer-causing gene produces a protein with elevated tyrosine kinase activity that induces the onset of leukemia12. Researchers were able to use the Philadelphia chromosome as a biomarker to indicate which patients would benefit from drug candidates (tyrosine-kinase inhibitors) specifically targeting the rogue protein. The end product was the drug imatinib (Gleevec), which decreases the proliferation of Philadelphia chromosome cells and slows the progression of the disease. As a postscript to this story, researchers further found that specific mutations in the BCR– ABL gene were biomarkers that predicted resistance to imatinib, leading to the development of newer tyrosine-kinase inhibitors dasatinib and nilotinib.

HIV viral load: In the late 1980's, scientists discovered that HIV viral load could be used as a marker of disease progression, and subsequently, as a measure of antiretroviral treatment efficacy. Viral load was used to show that patients receiving combination therapy had a higher reduction in viral load than those on immunotherapy, and was therefore more effective in slowing the progression of the disease. Eventually, the viral load biomarker was used in the development and assessment of Highly Active Antiretroviral Therapy (HAART) treatment regimens involving a combination of several drugs used by many people living with HIV today.

HER-2 gene and receptor: Probably the most famous biomarker in recent drug development history is the HER-2 gene and receptor, discovered in the mid 1980's. Between 20–30% of breast cancer patients show an over-expression of the HER-2 receptor on their cancer cells. Although this biomarker indicates a higher risk of adverse outcomes, it also gave clinicians a new target for novel therapies. The antibody trastuzumab (Heretic) was developed to target HER-2 receptors in these overexpressing patients, and successfully reduces the proliferation of cancer cells in many of these women.[10,11]

Biomarkers are already embedded into our language and medical care today. Cardiovascular risk can be assessed through blood pressure and cholesterol checks. Diabetic patients can test their glucose levels using one test – haemoglobin A1C (HbA1c) – that provides glucose levels from the most recent two weeks. Liver function tests (LFT) assess liver toxicity and prostate-specific antigen (PSA) assesses prostate cancer risk and disease state. These common biomarkers have historically taken decades to become part of medical practice. For example, PSA is a biomarker for diagnosing and monitoring prostate disease, the most prevalent cancer in men. The 30-year evolution of PSA, illustrating how it took decades for PSA to evolve into an accepted biomarker and finally be used to help develop new therapies. PSA evolution and use reveals some common themes in biomarker lifestyle. This progress came from 30 years of one biomarker's evolution. Biomarker development should follow different pathways depending on the stage of drug development. For early stages of clinical development, biomarkers can identify or confirm molecular targets, help to optimize dose schedules for the anticancer agent and might correlate with clinical benefit. Identifying clinically relevant targets is challenging; in numerous examples, the intended target was found to be irrelevant. As not all molecular targets are legitimate therapeutic targets, however, biomarkers can provide a means of determining which target(s), when inhibited, correlate with tumour control. In the case of some anticancer agents [e.g. cetuximab, gefitinib, erlotinib and inhibitors of vascular endothelial growth factor (VEGF)]; it appears that the molecular target is the therapeutic target. In the later stages of clinical development, identified markers could be used to select the patients most likely to respond to the targeted agent. Any biomarker used as a basis for patient otherwise, the risk of not treating patients who might benefit would be unacceptably high. Proper patient selection enables efficient clinical trial design for targeted therapies and ensures that the number of individuals exposed to the risks of anticancer therapy is minimized.[12,13]

3. CLASSIFICATION BIOMARKERS:

Biomarkers can be classified based on different parameters. They can be classified based on their characteristics such as:

Imaging biomarkers (CT, PET, and MRI) or molecular biomarkers. Molecular biomarkers can be used to refer to non-imaging biomarkers that have biophysical properties, which allow their measurements in biological samples (example, plasma, serum, cerebrospinal fluid, bronchoalveolar cleavage, and biopsy) include nucleic acids-based biomarkers such as gene mutations or polymorphisms and quantitative gene expression molecules.[14]

Another category of biomarkers includes those used in decision making in early drug development. For instance, pharmacodynamic (PD) biomarkers are markers of a certain pharmacological response, which are of special interest in dose optimization studies.[15]

Biomarkers based on genetic and molecular biology methods can be classified into three types.-Type 0 - Natural history markers**,** Type 1 - Drug activity markers **,**Type 2 - Surrogate markers.

- **Type 0- Natural history markers***:* A marker of natural history of a disease and correlates longitudinally with known clinical indices.
- **Type 1- Drug activity markers***:* A marker that captures the effect of a therapeutic intervention in accordance with its mechanism of action.
- **Type 2- Surrogate markers***:* A marker intended to substitute for a clinical end point; a surrogate end point is expected to predict clinical benefit or lack of benefit on the basis of epidemiology, therapeutic, Patho physiological or other scientific evidence.[16]

Biomarkers based on drug development can be describe as Diagnostic biomarkers provide the means to define a population with a specific disease. (i.e., cardiac troponin for the diagnosis of myocardial infraction.). Prognostic biomarkers correlate with outcomes. For example, over expression of Her-2/neu in breast cancer or EGFR expression in colorectal cancer indicates poor prognoses. Such prognostic markers are frequently the basis for establishing inclusion criteria for a clinical trial or for defining a patient population. It is also know as cancer biomarkers, and biomarkers for monitoring the clinical response to an intervention (HbAlc for ant diabetic treatment). Predictive biomarkers define populations that might respond more favourably to a particular intervention from an efficacy or safety perspective. They can be used to stratify patients for subgroup analyses.[17]

4. BIOMARKERS REQUIREMENT:

For chronic diseases, whose treatment may require patients to take medications for years, accurate diagnosis is particularly important, especially when strong side effects are expected from the treatment. In these cases, biomarkers are becoming more and more important, because they can confirm a difficult diagnosis or even make it possible in the first place.[18] A number of diseases, such as Alzheimer's disease or rheumatoid arthritis, often begins with an early, symptom-free phase. In such symptom-free patients there may be more or less probability of actually developing symptoms. In these cases, biomarkers help to identify high-risk individuals reliably and in a timely manner so that they can either be treated before onset of the disease or as soon as possible thereafter.

In order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible. This may be a blood sample taken by a doctor, a urine or saliva sample, or a drop of blood like those diabetes patients extract from their own fingertips for regular blood-sugar monitoring. For rapid initiation of treatment, the speed with which a result is obtained from the biomarker test is critical. A rapid test, which delivers a result after only a few minutes, is optimal. This makes it possible for the physician to discuss with the patient how to proceed and if necessary to start treatment immediately after the test. Naturally, the detection method for a biomarker must be accurate and as easy to carry out as possible. The results from different laboratories may not differ significantly from each other, and the biomarker must naturally have proven its effectiveness for the diagnosis, prognosis, and risk assessment of the affected diseases in independent studies.[12,19]

5. CHARACTERISTICS OF BIOMARKERS:

An ideal biomarker should be safe and easy to measure. The cost of follow-up tests should be relatively low, there should be proven treatment to modify the biomarker. It should be consistent across genders and ethnic groups. If the biomarker is to be used as a diagnostic test, it should be sensitive and specific and have a high predictive value.[20] A highly sensitive test will be positive in nearly all patients with the disease, but it may also be positive in many patients without the disease. To be of clinical value, a test with high sensitivity should also have high specificity, in other words, most patients without the disease should have negative test results. For predicting the likelihood of disease based on the test result, rather than the converse, the appropriate measures are positive and negative predictive values. Unfortunately, the positive predictive value falls as the prevalence of the disease falls, so tests for rare conditions will have many more false positive results than true positive result.

6. DISEASE-RELATED BIOMARKERS AND DRUG-RELATED BIOMARKERS:

- It is necessary to distinguish between disease-related and drug-related biomarkers. Disease-related biomarkers give an indication of whether there is a threat of disease (risk indicator or predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case (prognostic biomarker). In contrast, drug-related biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it.

- In addition to long-known parameters, such as those included and objectively measured in a blood count, there are numerous novel biomarkers used in the various medical specialties.

- Currently, intensive work is taking place on the discovery and development of innovative and more effective biomarkers. These "new" biomarkers have become the basis for preventive medicine, meaning medicine that recognises diseases or the risk of disease early, and takes specific countermeasures to prevent the development of disease. Biomarkers are also seen as the key to personalised medicine, treatments individually tailored to specific patients for highly efficient intervention in disease processes. Often, such biomarkers indicate changes in metabolic processes.

- The "classic" biomarker in medicine is a laboratory parameter that the doctor can use to help make decisions in making a diagnosis and selecting a course of treatment. For example, the detection of certain auto antibodies in patient blood is a reliable biomarker for autoimmune disease, and the detection of rheumatoid factors has been an important diagnostic marker for rheumatoid arthritis (RA) for over 50 years.[19,21] For the diagnosis of this autoimmune disease the antibodies against the bodies own citrullinated proteins are of particular value. These ACPAs, (ACPA stands for *A*nti-*c*itrullinated *p*rotein/peptide *a*ntibody) can be detected in the blood before the first symptoms of RA appear. They are thus valuable and highly predictive biomarkers for the early diagnosis of this autoimmune disease. In addition, they indicate if the disease threatens to be severe with serious damage to the bones and joints,[22] which is an important tool for the doctor when providing a diagnosis and developing a treatment plan.

There are also more and more indications that ACPAs can be very useful in monitoring the success of treatment for rheumatoid arthritis.[23] This would make possible the accurate use of modern treatments with biological. Physicians hope to soon be able to individually tailor rheumatoid arthritis treatments for each patient. With the growing number of new biological agents, there is increasing pressure to identify molecular parameters such as ACPAs that will not only guide the therapeutic decision but also help to define the most important targets for which new biological agents should be tested in clinical studies.[24]

An NIH study group committed to the following definition in 1998: "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." In the past, biomarkers were primarily physiological indicators such as blood pressure or heart rate.

More recently, biomarker is becoming a synonym for molecular biomarker, such as elevated prostate specific antigen as a molecular biomarker for prostate cancer, or using enzyme assays as liver function tests. There has recently been heightened interest in the relevance of biomarkers in oncology, including the role of KRAS in CRC and other EGFR-associated cancers. In patients whose tumours express the mutated KRAS gene, the KRAS protein, which forms part of the EGFR signalling pathway, is always 'turned on'. This overactive EGFR signalling means that signalling continues downstream – even when an EGFR inhibitor, such as cetuximab (Erbitux) – and results in continued cancer cell growth and proliferation block the upstream signalling. Testing a tumour for its KRAS status (wild-type vs. mutant) helps to identify those patients who will benefit most from treatment with cetuximab.

7. BIOMARKERAS AN EMERGING TOOL:

7.1 Biomarker in Drug Development:

Biomarkers are useful throughout the drug discovery and development process. In the past, biomarkers have tended to appear in drug development programmes as opportunists – taking advantage of spare samples and leftover money in the budget – often resulting in incomplete or inadequate data. However, they are now becoming more and more integrated into all stages of the development process, ranging from:

- Target discovery
- Evaluation of drug activity
- Understanding mechanisms of action
- Toxicity and safety evaluation
- Internal decision making
- Clinical study design
- Diagnostic tools
- Understanding disease processes

Biomarkers can be of varying types, such as physiological, physical, anatomical and histological (tissue biopsy specimens). Perhaps the most relevant type for early phase clinical research is biochemical biomarkers, derived from bodily fluids that are easily available to the early phase researchers. The use of pharmacodynamic markers in drug development, typically blood based biomarkers that are influenced by drugs, is a fresh approach.[25]

- Once a proposed biomarker has been validated, it can be used to diagnose disease risk, presence of disease in an individual, or to tailor treatments for the disease in an individual (choices of drug treatment or administration regimes).
- In evaluating potential drug therapies, a biomarker may be used as a surrogate for a natural endpoint such as survival or irreversible morbidity. If a treatment alters the biomarker, which has a direct connection to improved health, the biomarker serves as a surrogate endpoint for evaluating clinical benefit.
- Some of the main areas in which molecular biomarkers are used in the drug development process are, early drug development studies, safety studies, proof of concept studies, molecular profiling.
- Molecular biomarkers are often used in early drug development studies. For instance, they are used in phase-I

study for establishing doses and dosing regimen for future phase II studies. PD biomarkers are commonly observed to respond (either decrease or increase) proportionally with dose. This data, in conjunction with safety data, help determine doses for phase II studies.

- In addition, Safety molecular biomarkers have been used for decades both in preclinical and clinical research. Since these tests have become mainstream tests, they have been fully automated for both animal and human testing.[4] Among the most common safety tests are those of liver function(e.g., transaminases, bilirubin, alkaline phosphates) and kidney function(e.g., serumcreatinine, creatinine clearance, cystatin C). Others include markers of skeletal muscle (e.g., myoglobin) or cardiac muscle injury (e.g., CK-MB, troponin I or T), as well as bone biomarkers (e.g., bone-specific alkaline phosphates).
- Biochemical and molecular markers have revolutionized medicine and drug development in recent decades, giving clinicians and researchers the opportunity to infer biological states in patients and in response to drug interventions. For example, the blood of HIV patients can be tested for its viral load to assess the course of their disease, as well as providing a surrogate endpoint for trials of anti-HIV drugs.
- Biomarker studies will eventually become an integral part of the drug development process. The ultimate aim is the development of more effective drugs at a lower cost. Although still at early stages and with many issues to be resolved, the outlook for biomarkers is promising.
- The clinical development of gefitinib, an orally available epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is a more complex example of biomarker development.
- Evolution of biomarkers during the conduct of large randomized trials might become the rule rather than the exception. Although initial candidate biomarkers are evaluated early in development, knowledge increases exponentially as research and clinical experience become more widespread and increased clinical data with which to correlate the translational work become available.[26-29]

7.2 Biomarker in Diseases

Biomarkers depicting prodromal signs enable earlier diagnosis or allow for the outcome of interest to be determined at a more primitive stage of disease. Blood, urine, and cerebrospinal fluid provide the necessary biological information for the diagnosis. In these conditions, biomarkers are used as an indicator of a biological factor that represents either a subclinical manifestation, stage of the disorder, or a surrogate manifestation of the disease.

- Biomarkers used for screening or diagnosis also often represent surrogate manifestations of the disease.
- The potential uses of this class of biomarkers includes, Identification of individuals destined to become affected or who are in the “preclinical” stages of the illness, reduction in disease heterogeneity in clinical trials or epidemiologic studies, reflection of the natural history of disease encompassing the phases of induction, latency and detection, target for a clinical trial. The improvement in validity and precision far outweigh the difficulty in obtaining such tissues from patients.
- Diagnostic tests for diseases are used with increased frequency in clinical research and practice. In the diagnostic effort, collection of information from various sources, some of which includes results from diagnostic tests, helps to achieve the ultimate goal of increasing the probability of a given diagnosis. Clinical tests are also performed, though probably less often, for other reasons such as the following: to measure disease severity, to predict disease occurrence, or to monitor the response to a particular treatment.[30]

- More importantly, biomarkers for disease easily lend themselves to clinical trials. Another advantage of this type of diagnostic test is the reduction in disease heterogeneity in clinical trials or observational epidemiologic studies, leading to better understanding of natural history of disease encompassing the phases of induction, latency and detection.[31.]

- The use of biomarkers is growing, with a steady stream of new products being brought out by the diagnostics industry. Some of these assist in diagnosis, while others provide a means of monitoring the state of progression of disease and the effectiveness of therapeutic options. However, in many cases, the evidence which supports the use of these new methods as opposed to traditional biochemical tests has not yet been demonstrated, and it is intended that this volume will help clarify the strengths and weaknesses of using these biomarkers across a wide range of applications and in the various organs of the body. This approach will provide clinicians, pathologists, clinical biochemists and medical laboratory scientists with an invaluable overview of the diverse applications of biomarker in medicines.[29]

- Biomarkers of all types have been used by generations of epidemiologists, physicians, and scientists to study human disease. The application of biomarkers in the diagnosis and management of cardiovascular disease, infections, immunological and genetic disorders, and cancer are well known. Their use in research has grown out of the need to have a more direct measurement of exposures in the causal pathway of disease that is free from recall bias, and that can also have the potential of providing information on the absorption and metabolism of the exposures.[32] Neuroscientists have also relied on biomarkers to assist in the diagnosis and treatment of nervous system disorders and to investigate their cause. Blood, brain, cerebrospinal fluid, muscle, nerve, skin, and urine have been employed to gain information about the nervous system in both the healthy and diseased state. This paper focuses on biomarkers as defined by Houlka i.e., direct measures of biological media, and other papers in this issue will address brain imaging and other markers.

The rapid growth of molecular biology and laboratory technology has expanded to the point at which the

application of technically advanced biomarkers will soon become even more feasible.[33-35] Molecular biomarkers will, in the hands of clinical investigators, provide a dynamic and powerful approach to understanding the spectrum of neurological disease with obvious applications in analytic epidemiology, clinical trials and disease prevention, diagnosis, and disease management.

7.3 Imaging Technologies:

- Biomarkers are measures of a normal biological process in the body, a pathological process, or the response of the body to a therapy. Imaging-based biomarkers employ a variety of technologies to capture images of anatomical and physiological changes in the body.
- Many new biomarkers are being developed that involve imaging technology. Imaging biomarkers have many advantages. They are usually noninvasive, and they produce intuitive, multidimensional results. Yielding both qualitative and quantitative data, they are usually relatively comfortable for patients. When combined with other sources of information, they can be very useful to clinicians seeking to make a diagnosis.
- Another new imaging biomarker involves radiolabel fludeoxyglucose; Positron emission tomography (PET) can be used to measure where in the body cells take up glucose.

7.3.1 X-Ray:

In clinical settings, x-rays are emitted towards the body, passing through it and creating an image recorded onto film, or more recently, digitally. X-ray technology has been in use for over 100 years and has served to identify structural markers in biomedicine for almost as long.

7.3.2 Computed Tomography (CT):

Sometimes also called computed axial tomography (CAT scan), in this technique x-rays are used to take a series of 2-dimensional images which are then digitally converted to a 3-dimensional image. CT was introduced during the 1970s and its use has expanded widely.

7.3.3 Magnetic Resonance Imaging (MRI):

No ionizing radiation is used. Instead, the subject is placed in a powerful magnetic field which aligns the nuclear magnetic field of atoms, usually hydrogen atoms in the body's water. Radio frequency signals are used to alter the atoms' magnetic alignment and the resulting signal is detected by scanners. MRI is better at distinguishing soft tissues than tomography. The first MR image was published in 1973, the first cross-sectional image of a living mouse in 1974, and the first studies performed on humans were published in 1977. In addition, optical imaging is frequently used in drug discovery and pre-clinical animal research, and is increasingly used in the clinic for humans, for example with optical CT scanning. Ultrasound (US) is also often used in the clinic and recently has been explored as a method to deliver drugs.

7.3.4 Positron Emission Tomography (PET)

A short-lived radioactive tracer isotope, fluorine (^{18}F) for example, is injected into the body, usually attached to a probe molecule that accumulates in the tissue of interest. The isotope emits a positron (an anti-electron) which travels a short distance before colliding with an electron. The collision annihilates the two particles and emits two gamma rays travelling in opposite directions which are detected by a scanner. Computerized tomography assembles a 3-dimensional image of the area of interest. The first PET machines for use in humans were introduced in early 1970.[36]

7.4 Diseases and Treatments:

7.4.1 Markers of Disease in Prostate Cancer:

There are no reliable biomarkers for disease progression in aggressive prostate cancer that has demonstrated utility in product development. Although prostate specific antigen (PSA) is used for a variety of purposes (e.g., determining when further diagnostic testing is indicated, assessing response to therapy), there is no consensus on how best to use PSA in cancer therapeutic trials. Uses of PSA that should be further investigated including identifying high-risk populations, providing an early marker of drug activity and dose range, and use of PSA as a marker of disease progression. Other markers may also prove more predictive of clinical outcomes in some patients (e.g., alpha methyl aryl CoA racemes expression as a predictor of disease progression in local disease). A gap analysis to rigorously identifying what is proven and unproven about PSA and other potential indicators would be an important first step to improving prostate cancer biomarkers.

7.4.2 Markers of Disease Activity in Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Related Diseases:

Development of new therapies for these diseases has been hampered in recent years by a lack of reliable markers of disease activity that can be used to predict clinical benefit. Development of predictive biomarkers and accepted clinical outcome measures would help in the evaluation of needed new therapies for these diseases.

7.4.3 Biomarkers in Arthritis:

Targeted research could identify how to apply MRI technologies to measure the effects of potential therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis. In this regard, MRI has demonstrated promise for detecting soft tissue inflammation and cartilage erosion in rheumatoid arthritis. If established as a reproducible biomarker, use of MRI could help determine the potential of a new therapeutic product, identify dose ranges, and stratify patients by risk while serving as an early response measure.

7.4.4 Biomarkers in Cardiovascular Diseases:

To advance efficient development of new therapies, new imaging techniques are needed to measure progression and treatment of cardiovascular disease. Examples include the

potential use of intravascular ultrasound (IVUS), MRI, or multi-slice CT in the assessment of atherosclerosis progression and volumetric measures of cardiac function in trials of congestive heart failure. Development of these techniques for measuring progression will require a complete analysis of the current state of knowledge of the imaging modality, standardization of the technical aspects of the measurement, and performing the trials necessary to evaluate the degree of correlation with clinical responses.

7.4.5 Biomarkers in Chronic Obstructive Pulmonary Diseases:

High-resolution chest computed tomography might be a useful assessment of disease progression in chronic obstructive pulmonary disease where emphysema is a prominent component, especially the disease associated with alpha 1 anti-trypsin deficiency. Although data to date suggest that high resolution CT (HRCT) can offer reliable assessment of underlying lung structure in fewer patients and for shorter periods of time than would be needed to show a difference in lung function testing or in mortality, it remains unclear if changes in HRCT meaningfully predict change for the patient. It also is unclear what level of change in the HRCT parameters could be considered significant in terms of disease modification. The ability to use HRCT demonstration of disease modification as an endpoint in clinical trials could pave the way for new product indications that are now infeasible due to the rarity of alpha 1 anti-trypsin deficiency and the trial size and duration needed to show an effect using traditional endpoints. New trials, perhaps with innovative designs, are needed to evaluate the use of imaging techniques in rare conditions.

7.4.6 Imaging Biomarkers in Neurocognitive Diseases:

Currently, therapeutic trials in chronic neurological disorders, such as Parkinson's disease and Alzheimer's disease, rely on symptomatic endpoints that may require observation over many years to evaluate progression. Functional imaging, such as FDG-PET as a measure of glucose metabolism, may provide a biomarker to assess earlier, more subtle, changes in the progression of these diseases. Studies would be needed to determine how these markers correlate with symptomatic progression. Focused efforts to apply new imaging techniques as diagnostic and response measures in neurocognitive disorders and depression could also produce new ways to monitor treatment of these conditions. For example, quantitative MRI measurements as well as amyloidal content assessments by PET scan may be useful imaging techniques to demonstrate the effect of potential Alzheimer's therapies. Imaging markers that provide information on early disease states could make prevention trials more feasible.[37]

8. CONCLUSION:

Biomarker defined as alteration in the constituents of tissues or body fluids provide a powerful approach to understanding the spectrum of chronic disease with application in at least 5 areas like screening, diagnosis, prognostication, prediction of disease recurrence and therapeutic monitoring. Biomarkers have the potential to increase the efficiency aspects at many stages of drug and biomedical research. But there are challenges too as biomarker discovery is expensive and resource consuming. Furthermore, there are no standard or universal criteria on developing and validating biomarkers and Regulatory authorities will continue to ask for more and more biomarker related data during the drug approval process. Biomarkers offer great potential for empowering decision making at early stages of the drug development process, reducing drug development costs and shortening the drug development timeline. However, the sizeable investment of both time and money needed for biomarker research and development is hampering this progress. A biomarker may be specific for only one type of drug or disease, so the development costs will have to be carefully considered. Although initially the use of biomarkers will increase the cost of clinical development, in the long-term their use should lower the cost and duration of clinical development.

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